Washington State Department of Health
Newborn Screening for Cystic Fibrosis
Economic Analysis
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Cystic Fibrosis, an Overview

Cystic fibrosis (CF) is a chronic, progressive, life shortening genetic (inherited) disease of the body's mucus glands. It causes thick, sticky mucus to build up in the lungs, digestive system, and other organs. Accumulations of thick mucus in the intestines and lungs result in malnutrition, poor growth, frequent respiratory infections, breathing difficulties, and eventually permanent lung damage. Lung disease is the cause of death in most patients.

Various other CF related medical problems may include inflammation of the nasal sinuses, nasal polyps, clubbing of fingers and toes, rupture of lung tissue and trapping of air between the lung and chest wall, coughing of blood, heart enlargement, chronic abdominal pain and discomfort, gassiness, loose stools, and failure to thrive. Liver disease, diabetes, pancreatic inflammation, and gallstones also occur in some people with CF. Adults show more serious complications such as collapsed lung, heart failure, infertility and frequent infections that eventually lead to death.

Most people with CF must perform daily airway clearance therapy to help clear mucus from the lungs, take antibiotics to fight lung infections, take pancreatic enzyme supplements with each meal to absorb enough calories and nutrients, and take drugs to thin mucus and improve lung function.

Early diagnosis of CF through newborn screening increases the potential avoidance of severe complications from delayed diagnosis. It improves growth and physical development and increases the opportunity for early identification and treatment of pulmonary disease. It provides genetic counseling and emotional support for families and reduces newborn and infant mortality and the risk of malnutrition and low cognitive abilities. And, importantly, the difficult and stressful diagnostic odyssey that often occurs with undiagnosed CF can be avoided

Newborn screening provides the opportunity of timely use of the wide range of available treatments including enzyme replacements, supplemental salt, antibiotics to control infection, oxygen therapy, physical therapy, surgery and organ transplantation. Recent advances in care and treatment have improved the length and quality of life for people with CF. The median age of survival is now in the early to mid-30s

Cost-Benefit Analysis

Since newborn screening is supposed to reduce or eliminate pain and suffering for both patients and their families, qualitative benefits should be the basis of decision making for this type of screening. However, because of limited public resources and alternative ways of allocating this limited budget among promising programs, financial measures (indices) are also needed. Cost-benefit ratio and cost-effectiveness index are among those that are commonly used in the health sector.

The two approaches look at costs and benefits in different ways. Cost-effectiveness analysis looks at the costs of saving life. The net cost figure, defined as the difference between the costs and benefits of intervention, would be applied to years of life saved. Cost-benefit analysis includes the value of saving life in the benefit pool and compares it with the costs of intervention. Calculating these financial or semi-financial indices require estimation of benefits in quantitative terms. Most of these benefits are estimated in terms of cost offsets or costs averted as a result of intervention programs.

Data from the Washington State Department of Health (DOH) death database shows CF as the underlying cause for 7 deaths during the calendar year 2003 and an average annual of 9 deaths between 2000 and 2003 (Table 3). Data from the hospital discharge database indicates that CF related hospitalization cost more than $10 million during the calendar year 2004 and an average annual cost of $6 million between 2000 and 2003 (Table 5). In addition to the costs of hospitalization, the total medical costs of CF also include the costs of outpatient clinics and prescription drugs.

Applying medical cost distribution (hospital costs = 47%, Outpatient clinic costs = 12%, Medication costs = 41%) from Tracy Lieu's study (1) and using the 2004 hospital costs ($10,396,985 = 70% of hospital charge) as our base, the total medical costs of CF related treatment exceeded $22 million in the calendar year 2004. Adding the costs of life lost, pain and suffering, missing valuable time at school for children, and the costs associated with loss of working time for parents of sick children makes cystic fibrosis an expensive disease.

Early detection of CF through newborn screening can reduce these costs. It provides the opportunity to initiate intervention at an earlier age and increases the potential avoidance of severe complications from delayed diagnosis. Data indicate that newborn screening can result in lowered newborn and infant mortality, reduced costs of hospital care, and reduced risk of malnutrition and low cognitive abilities.

According to the most recent national newborn screening status report, published August 31, 2005 by the National Newborn Screening and Genetic Resource Center (NNSGRC), 19 states or 37% of the 51 reported states include cystic fibrosis in their newborn screening programs, applying it statewide or to limited populations. Screening for cystic fibrosis is universally required by law or rule in Colorado, Iowa, Mississippi, New Jersey, New York, Oklahoma, South Carolina, Wisconsin, and Wyoming. In Massachusetts, Montana, Pennsylvania screening for CF is universally offered but not required. Screening for CF is offered to selected populations in Connecticut and South Dakota and testing for CF is required but not implemented by Florida, Kentucky, Minnesota, New Hampshire, and Virginia.

Evidence suggests that early identification can make a difference in babies with CF. Without newborn screening, diagnosis is typically delayed beyond a year of age. Early diagnosis through newborn screening gives the opportunity for early intervention. The data show that babies who are treated early have improved nutritional status and cognitive development, and have reduced length of stays in hospitals and lowered mortality.

Cystic fibrosis is an important health problem that occurs frequently enough to justify population based screening of newborns in Washington State. The purpose of this cost-benefit / effectiveness analysis is to evaluate and compare the benefit-cost of newborn screening for cystic fibrosis (intervention) with the current costs of CF related disease (no intervention). The analysis looks at two screening protocols and compares their costs and benefits.

Methodology and Data

Decision analysis was used to compare the costs and benefits of newborn screening (intervention) with no intervention. Protocols used to screen newborns for CF begin with a test that measures Immunoreactive Trypsinogen (IRT) in dried blood spots drawn 1 to 2 days after birth. Infants who have an elevated IRT measurement need further testing. Although several different screening protocols are used for cystic fibrosis screening, our study compares the costs and benefits associated with 1) further testing by measuring IRT again, on a subsequent specimen (termed IRT/ITR) and 2) further evaluation by direct DNA testing (termed IRT/DNA).

The IRT/IRT protocol requires obtaining a second dried blood spot specimen at approximately two weeks of age (because a second specimen is routinely submitted at this age for infants born in our state, this would not require additional specimen collection costs). Elevated IRT values are more specific for CF at this age, because IRT values decrease quickly with age in infants who do not have CF. If the repeat IRT is elevated above a given cutoff level, the child is referred for diagnostic sweat testing (a test that measures the amount of salt in the sweat). Individuals with CF have more salt in their sweat than unaffected people. A sweat test of a given elevated level confirmed by a second elevated sweat test result, is considered diagnostic for CF

An alternative screening method is the IRT/DNA protocol in which a single elevated IRT test is followed by DNA analysis on the original blood spot specimen, detecting one or more specific mutations that cause CF. Those newborns with a positive elevated IRT test and one or more detected mutations are referred for sweat testing to make a definitive diagnosis of CF. This DNA testing identifies both individuals affected by CF (two mutations) and those who have only one mutation (carriers) and will not develop disease.

Infants with positive results on both the screening and diagnostic tests are “true positive” and have CF. True positives are then referred for clinic visits. Those with positive screening tests and negative diagnostic test are “false positives.” All screen positive infants are referred for genetic counseling.

Costs associated with newborn screening for CF consist of the costs of screening (IRT/IRT or IRT/DNA), diagnostic testing (sweat tests), clinic visits, and the genetic counseling. When considering the costs of newborn screening, we don’t include costs that would occur in the future for babies with CF who would be diagnosed based on clinical symptoms (the costs of sweat tests, first office visits, and genetic counseling for the true positive group). We assume that these costs associated with true positive cases are associated with having CF and not with the newborn screening.

We assume that the impacts of risk factors such as mortality or time-lag for symptom based diagnosis are not strong enough to affect the results of our analysis. However, we relax this assumption and include the costs of additional clinic visits for affected children that occur before they would be diagnosed because of symptoms. We assume that the costs of these increased clinic visits should be included as the costs of newborn screening since they are a direct result of earlier detection.

Some of the benefits of earlier detection are highly qualitative (reducing or eliminating pain and suffering for patients and their families), and are difficult to measure. The most convincing benefit of CF newborn screening is reducing the risk of chronic malnutrition and growth retardation.

Quantitative or measurable benefits associated with newborn screening (intervention) are defined as the preventable costs of CF related disease. These are future costs that can be avoided as a result of newborn screening program. Current costs of CF are estimated from societal perspective in this analysis and costs and benefits are presented in 2004 dollars.

Among medical costs, hospitalization is the only one estimated here because costs of physician visits and medications are not available (although we did make a modest adjustment for reduced 'diagnostic odysseys', see Future Benefits below). Hospitalization data are from the Washington State hospital discharge database. Hospital charges are discounted by 30% to represent the approximate true costs of hospitalization. Benefits, or future hospital cost avoidance of screening, were defined only for those 10 years and younger.

Although Wisconsin reported a 50% reduction in the number of sweat tests after implementing newborn screening for CF, we didn't include this possible savings in our analysis because this data is controversial among CF clinicians.

Among societal costs, only the costs of CF related deaths are estimated here. The costs of work hours lost to parents, although likely substantial, are not included here since there is no readily available estimate for the amount of time lost. The costs of symptoms, pain and suffering to children, which are significant, are also not included in this study because of a lack of available estimates.

The projected number of newborns to be screened were provided by the Department of Health (DOH), Office of Newborn Screening. The projection is based on 10 year birth estimates for Washington State by Office of Financial Management (OFM). The number presented in Table (1) is one tenth of the projected 10-year numbers.

Table (1), Projected Children to be Screened

	IRT/IRT	IRT/DNA
Number of newborns to be screened	79,058	79,058
Number of positive screen tests	68	377
Number of true positive , children with CF	25	25
Number of false positive results	43	352
Number of false negative results	0.62	0.56
Number of CF carriers detected	0	255

Results

Costs – Screening

The laboratory costs of CF newborn screening varies depending on the protocol used. Table (2) shows the costs of the two screening tests, diagnostic sweat test, office visits, and the costs of genetic counseling for the projected number of newborns to be screened. The unit costs of population-base IRT/IRT and IRT/DNA tests in Washington State are estimated at $3.68 and $6.95 respectively, according the DOH, Office of Newborn Screening.

As mentioned, we do not include the costs of sweat tests, first office visits, and genetic counseling for the true positive group in this cost-benefit analysis. As shown in Table (2), the total costs of newborn screening consisted of the costs of screening, sweat tests and genetic counseling for the false positive group, and the costs of the additional office visits within the first year of life for the true positive group.

Table (2), Estimated Costs of Screening for Projected Number of Newborns

	IRT/IRT	IRT/DNA
Screening		
No. of projected NBS	79,058	79,058
Unit costs of screening	$3.68	$6.95
Costs of screening	**$290,933**	**$549,453**
Sweat Tests		
Unit costs of sweat test	$172	$172
No. of first sweat tests (false positives only)	43	352
No. of sweat tests including repeats due to age	56	427
Costs of sweat tests	**$9,666**	**$73,427**
Office Visits		
Unit costs of first office visit	$123	$123
Unit costs of second office visit	$88	$88
No. of first office visits	0	0
2-nd or more office visits (true positives only)	254	254
Costs of office visits	**$22,352**	**$22,352**
Genetic Counseling		
Unit costs of genetic counseling	$94	$94
No. of genetic counseling (false positives only)	43	352
Costs of genetic counseling	**$4,004**	**$33,041**
Total Costs of screening	**$326,956**	**$678,273**

Future Benefits: Reduction in Number of Office Visits (Diagnosis Odyssey)
The median age of clinical diagnosis on the basis of signs and symptoms other than meconium ileus (a CF caused bowel blockage present at birth that leads to rapid diagnosis) is 14.5 months. With the exception of meconium ileus, symptom-based diagnosis of CF is difficult because most of these symptoms are not specific to CF. Misdiagnoses of CF patients can result in multiple office visits, diagnostic tests and hospitalizations. This process has been referred to as "diagnostic odyssey" and can be very costly to the health-care system.

Early detection of CF through newborn screening may reduce or eliminate the excessive utilization and costs of these health care services. We use the $22,352 costs of the second and all follow–up visits as the costs associated with diagnostic odyssey and consider it as a future benefit of newborn screening in our analysis.

Future Benefits: Reduction in Cystic Fibrosis Related Death

Table (3) shows the number of cystic fibrosis (CF) related deaths for the years 2000 - 2003 in Washington. CF is listed as the underlying cause of death and also as a contributing cause of death in the table. As the table indicates, the number of CF-related deaths has dropped over time.

Table (3), Washington Residents CF Related Death Record
Source: DOH Death Database

Year	CF as Underlying cause of death	CF as Contributing cause of death	Total
2000	11	0	11
2001	10	1	11
2002	10	0	10
2003	7	0	7

Early detection of CF through newborn screening and proper treatment at an earlier age can reduce the number of CF-related deaths, particularly for younger children. Estimation of total mortality reduction requires estimating its two components: the differential in child survival and the extension in longevity. Interpolation of the survival graph based on analysis of the CF Foundation Patient Registry data (US), for those with 10 years follow-up, suggests a 1% higher survival rate for those detected by newborn screening compared to those detected by symptoms (5% deaths among NBS and 6% among non-NBS children). On the other hand, the findings of studies from other countries suggest 5-10% survival rates between the screened and unscreened groups. We assumed 2% mortality reduction rate in our analysis and used 1% and 5% when examining the sensitivity of our results.

Longevity extension suggests how many additional years of life an individual is assumed to live if their death in early childhood is averted. Assuming life expectancy would be the same for all

individuals with CF, which is currently 34 years in the US, it implies an extension of 30 life years. Using 3% or 4% discount rates, the present discounted values of the 30 extended years are 20.6 or 18.3 years respectively.

Value of life is frequently used in economic impact and cost-benefit analysis (2, 3, 4, and 5). The value of a statistical life is large and ranges from $1 to $16 million. The values are based on cost of illness, wage, risk studies, and willingness to pay. The values cluster in the $3 million to $7 million range and $4 million has been used frequently as an acceptable statistical average value of life in the US. Assuming $4 million for value of life in the US and 34 years life span of CF patients, we use the $117,647 as the average annual value of life in our analysis.

The number of life years saved for the 25 CF patients projected to be born each year is determined by our assumptions. Table (4) shows the estimated number of life years saved, the estimated value of life years saved based on assumptions regarding mortality reduction rates (1%, 2%, 5%)and discount rates (3%, 4%). For example, assuming a 2% mortality reduction rate and 3% discount rate, the total number of life years saved is 10.3 and the value of life years saved is $1,211,764 as are shown in the first numerical column of Table (4).

Table (4), Life Years Saved and their Estimated Values Based on Different Assumptions

Mortality Reduction Rate	2%	2%	1%	1%	5%	5%
Extended Life Years	30	30	30	30	30	30
Discount Rate	3%	4%	3%	4%	3%	4%
Discounted Extended Life Years	20.6	18.3	20.6	18.3	20.6	18.3
No. of CF cases	25	25	25	25	25	25
Total Life Years Saved	10.3	9.2	5.2	4.6	25.8	22.9
Annual Value of Life	117,647	117,647	117,647	117,647	117,647	117,647
Total Value of Life Saved	1,211,764	1,082,352	611,764	541,176	3,035,293	2,694,116

A. **Future Benefits – Reduction in Hospitalization**

Tables (5) presents aggregate hospital statistics for CF patients for calendar years 2000 to 2004 and detailed statistics for the year 2004 by CF diagnoses and age group. The table indicates that CF related hospitalization costs more than $10 million during the calendar year 2004 and an average annual of $6 million between 2000 and 2003. Early detection of CF through newborn screening and proper treatment at an earlier age may reduce the number of CF-related hospitalizations, particularly for younger children.

The reported findings of CF studies suggest a relatively high difference in hospital use between screened and unscreened CF populations. Reductions reported in the literature on the number of hospital days saved as a result of screening ranges from 8 days (RCTrial, Wales) to 23 days

(Cohort, Australia) and reduced hospital use ranges from 17% (RCTrial, Wisconsin) to 37% (Cohort, France).

The findings of the French cohort study (Reference 5) indicate that the screened group averaged 0.49*4.2=2.08 hospitalizations per child (49% had at least one hospitalization, and those that did had an average of 4.2 admissions) while the unscreened group averaged 0.87*3.5=3.01 hospitalizations per child. (87% had at least one hospitalization, and those that did had an average of 3.5 admissions), suggesting a reduction of one hospitalization episode per child over 10 years of screening. We use this reduction of one hospitalization episode per child as our savings (avoidable because of screening) in our analysis and apply it to hospital costs for those up to 10 years of age.

Table (5) shows two columns for average length of stay (Unduplicated Avg. Days, Duplicated Avg. Days). The unduplicated column represents average length of stay per hospital admission. In this case a patient's multiple hospital admissions are considered each as a separate admission for different patients. The denominator here is the number of hospitalization episodes and not the number of patients.

On the other hand, the denominator for the duplicated average length of stay is the number of patients, i.e.: the average days of hospitalization per patient.

Applying the results of the French study (reduction of one hospital admission per child) to Washington State data (10 days of hospitalization per admission on average for those up to 10 years of age for the year 2004), 250 hospitalization days are expected to be saved for the 25 true positive (TP) cystic fibrosis patients. Using the $2,672 average daily costs of hospitalization for this age group, a total of $667,958 is expected to be saved in hospitalization costs as a result of newborn screening.

Table (5), Hospital Inpatient Service Utilization and Costs
Source: DOH Hospital Discharge Database

Calendar Year	Diagnosis Descriptions	Age Groups	No. of Patients	Total Days	Unduplicated Avg Days	Duplicated Avg Days	Total Costs	Daily Avg Costs
2000			219	3,954	8.2	18.1	6,726,401	1,701
2001			222	3,603	7.6	16.2	6,815,861	1,892
2002			212	3,218	7.4	15.2	6,170,095	1,917
2003			202	3,183	7.8	15.8	6,863,303	2,156
2004			214	3,883	8.1	18.1	10,396,985	2,678
2004	With Pulmonary		118	2,308	8.7	19.5	6,434,206	2,788
2004	With Gastrointestinal		36	811	10.0	22.5	1,921,659	2,369
2004	With Other		60	764	5.7	12.8	2,041,120	2,672
2004		10 or Less	42	572	10.0	13.6	1,528,289	2,672
2004		11 to 20	93	2,004	8.6	21.5	5,508,048	2,749
2004		21 to 30	49	747	6.4	15.2	1,830,821	2,451
2004		31 to 40	19	412	7.9	21.7	1,140,017	2,767
2004		40 or more	11	148	6.4	13.5	389,810	2,634

Cost and Benefit Comparison

Table (6) shows the results of cost-benefit analysis for CF newborn screening program. Benefits associated with screening (intervention) are mostly qualitative and can not be easily measured. Reduction in symptoms, pain and suffering are not included in this analysis. Quantitative and measurable benefits are defined as avoidable current costs of CF related disease. Reduction in loss of work hours to parents, and reduction in sweat tests are not included because of the unavailability of data. Hospital charges are included and discounted thirty percent to approximate the true costs of hospitalization.

The numbers for total benefits in the table, indicate that the proposed CF newborn screening program is cost effective from health plan / insurance point of view as well as from social prospective. The $690,310 (total benefits excluding value of life saved) without including the value of life years saved exceeds the costs associated with both ITR/IRT and IRT/DNA screening methods. The benefit-cost ratios suggest that Washington State gains $5.4 dollars for each dollar spent if uses the IRT/IRT screening model and $2.6 dollars for each dollar spent if it uses the IRT/DNA screening model

Table (6) Estimated Costs - Benefits of Screening for Cystic Fibrosis in Washington State

	IRT/IRT		IRT/DNA
No. of projected infants screened	79,058		79,058
Screening cost per infant	3.68		6.95
Costs of screening tests	290933		549453
Costs of sweat tests	9666		73427
Costs of office visits	22352		22352
Costs of genetic counseling	4004		33041
Total costs	**$326,956**		**$678,273**
Costs of diagnosis odyssey avoided	22,352		22,352
Value of hospitalization avoided	667,958		667,958
Total benefits excluding value of life saved	**690,310**		**690,310**
Estimated life years saved	9.2		9.2
Assuming 2% survival rate and 4% discount rate			
Estimated value of life per year	117,647		117,647
Value of life saved	1,082,352		1,082,352
Total benefits including value of life saved	**1,772,662**		**1,772,662**
Net Benefits	1,445,706		1,094,390
Benefit cost ratio	5.4		2.6

Concluding Remarks

The findings of this cost-benefit analysis suggest that the Washington State proposed newborn screening program for cystic fibrosis is cost effective and is a valuable social investment. The findings show that the program not only is cost effective from a societal point of view but also is cost effective from the insurance and health care costs viewpoint. Savings in the costs of hospitalizations and diagnosis odyssey are sufficient enough to offset the total costs of the screening program. We used 2% survival rate and 4% discount rate in calculating the value of life years saved in this analysis. Changing our assumptions with regard to survival rates(1% - 5%) and/or discount rate (3% , 4%) as shown in Table (4) would change the value of life years saved but does not affect the cost effectiveness of the newborn screening program.

References:

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